26. (**Amended**) An oligonucleotide probe of claim 25, wherein each iterated unit comprises a string of universal nucleotides and/or nucleotide analogs followed by one or more designate nucleotide and/or nucleotide analog.

30. (**Canceled**)

REMARKS:

Applicants note with appreciation that the Examiner has withdrawn all rejections under 35 U.S.C. § 102. Applicants acknowledge and agree with Examiner's renumbering of claims 13-23 as 20-30.

Upon entry of this amendment, claims 1-4, 6-8, 10-12 and 20-29 are pending.

Claim 4 is amended by incorporating the elements presented in claim 30, and claim 30 is canceled without prejudice. Claims 7 and 8 are also amended by incorporating language similar to that formerly presented in claim 30. Claim 9 is canceled without prejudice. Claim 20 is amended merely to correct a grammatical error. Claims 21 – 24 and 26 are amended to correct the number of the claim from which each depends. In canceling or amending any claim, Applicants reserve the right to pursue similar claims in this and any future application. No new matter has been introduced.

CLAIMS 1-4, 6-12 and 20-30 REJECTED UNDER 35 U.S.C. 103(a)

The Examiner alleges that the rejected claims are obvious in view of WO 90/04652 in combination with Loakes et al. The Examiner argues:

> The degeneracy reducing nucleotides of WO 90/04652 are not the same as the universal nucleotides [but]...It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the universal nucleotides of Loakes et al. as the degeneracy reducing nucleotides in the oligonucleotides of WO 90/04652. Universal nucleotides are able to bind any natural nucleotide in a sequence, therefore reducing the degeneracy required in the set of probes even farther than was possible by the disclosure of WO 90/04652. One of skill in the art would have been motivated to select universal nucleotides such as those disclosed by Loakes et al., in view of their universal pairing, and their limited interference in the hybridization of an oligonucleotide with its target sequence.

Applicants disagree with this rejection under 35 U.S.C. § 103(a). As correctly noted by the Examiner, the degeneracy reducing nucleotides of WO 90/04652 are not the same as the universal nucleotides of the present claims. The degeneracy reducing nucleotides of WO 90/04652 are designed to specifically pair with three of A, C, T or G, but not with the fourth. In other words, each position of the probes of WO 90/04652 is either "X" (meaning a designate nucleotide that specifically pairs with another nucleotide) or "not X" (the "degeneracy reducing form", which pairs with any base except the one that X normally pairs with).

Applicants maintain that the Examiner has failed establish that one of skill in the art would have had motivation to combine WO 90/04652 with Loakes et al., and therefore that the Examiner has failed to make a prima facie case of obviousness. As noted in *In re Napier*, 55 F.3d 610 (Fed. Cir. 1995), "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." A similar point was made in *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989), "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification" (quoting *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984)).

There is no teaching or suggestion in either Loakes et al. or WO 90/04652 to make the modification suggested by the Examiner. In fact, the sequencing methods disclosed in WO 90/04652 are entirely predicated on the use of "not X" type nucleotides. Applicants assert that the methods of WO 90/04652 could not have been performed with a universal nucleotide, and that the reference actually teaches away from the present invention. For example, methods for sequence reconstruction are set forth in WO 90/04652 at part III, beginning on page 15. Beginning at the top of page 19, the reference reads:

> The probe positions are *always* occupied by a base or the absence of a base [i.e. "not X"]. Recall from above that the probes can be represented by the notation, for example, A0AA000A. The 0's represent in this case represent [*sic*] either C, G, T, or a degeneracy-reducing analog thereof. *In other words, the 0's represent "not A's"*. The comparisons entail the determination of the truth value of a base (from the register) and a base or

> a negative of a base (from the probe being compared). For example, if the register entry is A and the probe entry is "not T", then the logical operation of *"A AND not T" is logically true.* Thus proper overlap exists. On the other hand, [if] the probe entry is "not A", then the logical operation of *"A AND not A" is logically false.* Thus the overlap is improper and the probe is rejected. (*emphasis added*)

Applicants maintain that the logical steps of the referenced method are workable only if the probes contain "not X" nucleotides. Note that if one attempts to modify the reference in the manner suggested by the Examiner, by substituting "any of A, C, T or G" (a representation of an exemplary universal nucleotide) for "not T" and "not A" in the algorithm above, then both logic statements are "A AND any of A , C, T or G" (true in both cases!). This means that if the referenced methods are modified to use an exemplary universal nucleotide instead of a "not X" nucleotide, it is impossible to distinguish a proper sequence from an improper sequence. Furthermore, no other method for deducing the proper sequence is disclosed in the reference. Accordingly, Applicants believe that WO 90/04652 fails to suggest the use of a universal nucleotide and fails to provide any method by which one would reconstruct a sequence using probes containing a universal nucleotide. The referenced method requires the non-universal "not X" nucleotide and, by implication, the reference teaches away from the use of a universal nucleotide.

The deficiencies of WO 90/04652 are not cured by Loakes et al. Loakes et al. is solely directed to methods for using nucleic acid probes to prime polymerase-driven nucleic acid synthesis. Loakes et al. provides no guidance for the use of a universal nucleotide in method such as that of WO 90/04652.

Therefore, Applicants request reconsideration and withdrawal of this rejection of all pending claims under 35 U.S.C. § 103.

CLAIMS 7-12 REJECTED UNDER 35 U.S.C. 103(a)

The Examiner further rejects claims 7-12 in view of Loakes et al. in view of Chetverin et al.

Applicants traverse this rejection for the same reasons described above. Nonetheless, to expedite prosecution and not in acquiescence to a rejection Applicants

request amendment of claims 4, 7 and 8, incorporating elements similar to those formerly presented in claim 30.

Applicants assert that the amendments and the arguments presented above obviate the rejection, and Applicants request reconsideration and withdrawal of the rejection.

CLAIMS WITH AMENDMENTS SHOWN

4. (**Amended**) A set of oligonucleotide probes, comprising a plurality of instances of a sequence of universal and designate nucleotides and/or nucleotide analogs, wherein the universal and designate nucleotides and/or nucleotide analogs are ordered in an iterative pattern, and wherein

(a) the pattern comprises a first string of universal nucleotides and/or nucleotide analogs followed by a first segment, and a second string of universal nucleotides and/or nucleotide analogs followed by a second segment,

(b) the first string and the second string each comprise a universal nucleotide and/or nucleotide analog, and

(c) the first segment and the second segment each comprise a designate nucleotide.

7. (**Twice Amended**) A set of oligonucleotide probes, comprising a plurality of instances of a sequence of universal and designate nucleotides and/or nucleotide analogs ordered in a pattern, wherein the probes are displayed on a solid support and wherein

(a) the pattern comprises a first string of universal nucleotides and/or nucleotide analogs followed by a first segment, and a second string of universal nucleotides and/or nucleotide analogs followed by a second segment,

(b) the first string and the second string each comprise a universal nucleotide and/or nucleotide analog, and

(c) the first segment and the second segment each comprise a designate nucleotide.

8. (**Twice Amended**) A sequencing array, comprising

a substrate, and

a set of oligonucleotide probes disposed thereon, wherein each probe comprises an instance of a pattern of universal and designate nucleotides and/or nucleotide analogs such that the set comprises a plurality of instances of the pattern, and wherein

(a) the pattern comprises a first string of universal nucleotides and/or nucleotide analogs followed by a first segment, and a second string of universal nucleotides and/or nucleotide analogs followed by a second segment,

(b) the first string and the second string each comprise a universal nucleotide and/or nucleotide analog, and

(c) the first segment and the second segment each comprise a designate nucleotide.

9. **(Canceled)**

20. **(Amended)** An oligonucleotide probe, comprising a sequence of universal and designate nucleotides and/or nucleotide analogs ordered in a pattern, wherein

(a) the pattern comprises a first string of universal nucleotides and/or nucleotide analogs, followed by a first segment, and a second string of universal nucleotides and/or nucleotide analogs followed by a second segment,

(b) the first and second strings each comprise two or more consecutive universal nucleotides and/or nucleotide analogs, and

(c) the first and second segments comprise at least one designate nucleotide [and or] and/or nucleotide analog.

21. **(Amended)** The probe of claim [13] 20, having a universal nucleotide and/or nucleotide analog selected from the group consisting of 5-nitroindole and 3-nitropyrrole.

22. **(Amended)** The probe of claim [13] 20, further comprising at least two contiguous designate nucleotides and/or nucleotide analogs bound to an end of the sequence.

23. (**Amended**) The probe of claim [13] 20, wherein the universal and designate nucleotides and/or nucleotide analogs are linked by analogs of phosphodiester bonds.

24. (**Amended**) The probe of claim [13] 20, wherein the universal and designate nucleotides and/or nucleotide analogs are peptide nucleic acids.

26. (**Amended**) An oligonucleotide probe of claim [14] 25, wherein each iterated unit comprises a string of universal nucleotides and/or nucleotide analogs followed by one or more designate nucleotide and/or nucleotide analog.

30. (**Canceled**)

Conclusion

For the reasons given above, Applicants respectfully request reconsideration of this application and timely allowance of the pending claims. Applicants submit that the pending claims, as amended, are in condition for allowance. If the Examiner believes that a personal or telephonic interview would expedite allowance of these claims, he is invited to call the undersigned.

If there are any fees, such as excess claims fees, due in connection with the filing of this Response, please charge the fees to our Deposit Account No. 06-1448. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
FOLEY, HOAG & ELIOT

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